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Tumor-infiltrating T lymphocyte clonality predicts prognosis in human ovarian cancer

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Background

The prognostic significance of the number of tumor-infiltrating T cells has been demonstrated for many tumor types. In contrast, the significance of the tumor-infiltrating T cell clonality, which reflects the preferential infiltration or expansion of T cell clones in the tumor microenvironment, has not been clear because of the technical hurdles required for evaluating each T cell clone in the tumor. In order to delineate the complexity of T cell responses and define correlates of a protective immunity, we applied a recently developed deep T cell receptor (TCR)-sequencing technology (immunoSEQ) to paired frozen tumor tissues and peripheral blood mononuclear cells from 99 ovarian cancer patients.

Methods

Rearranged β TCR chain DNA sequences were sequenced using immunoSEQ technology. Frequency of each T cell clone was obtained from the copy number of the sequence. T cell clonality of the specimens was calculated from entropy of TCR sequences. Spontaneous immune responses against tumor-associated antigens (NY-ESO-1, MAGE-A1, MAGE-A3 and p53) were evaluated by measuring serum antibodies by ELISA.

Results

Approximately $3(\pm3)\times10^6$and $4(\pm2)\times10^6$ full-length TCR beta chain sequences were obtained corresponding to the detection limit for T cell frequency at $3\times10^{-7}$and 2×10^{-7} for tumor and blood samples, respectively. In patients who had spontaneous antibodies against a panel of tumor-associated antigens, more clonal T cell infiltration was associated with longer progression-free survival. In sharp contrast, clonal infiltration was a worse prognostic factor in patients without detectable humoral immune responses against surrogate tumor antigens. From sequence based analyses, we found a set of shared TCR sequences among patients.

Conclusion

Deep TCR sequencing using immunoSEQ technology is a powerful tool to characterize tumor-infiltrating T cell clonality using frozen tumor tissues. Our analyses indicate that evaluation for spontaneous anti-tumor immune responses is required to correctly understand the prognostic significance of tumor-infiltrating T cells.

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